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Citrus Consumption and Risk of Cutaneous Malignant Melanoma in the Women's Health Initiative

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Abstract

Citrus products are rich sources of furocoumarins, a class of photoactive compounds. Certain furocoumarins combined with ultraviolet radiation can induce skin cancer. We examined the relationship between citrus consumption and cutaneous melanoma risk among 56,205 Caucasian postmenopausal women in the Women's Health Initiative. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of melanoma by citrus intake level. During a mean follow-up of 15.7 years, 956 incident melanoma cases were documented. In multivariable adjusted models, the HR (95% CI) for melanoma was 1.12 (0.91, 1.37) among the highest citrus consumers (1.5+ servings/day of fruit or juice) versus the lowest (<2 servings/week), 0.95 (0.76, 1.20) among the highest citrus fruit consumers (5+ servings/week) versus non-consumers, and was 1.13 (0.96, 1.32) for the highest citrus juice consumers (1+ servings/day) versus the lowest (<1 serving/week). In stratified analyses, an increased melanoma risk associated with citrus juice intake was observed among women who spent the most time outdoors in summer as adults; the HR for the highest versus lowest intake was 1.22 (1.02, 1.46) (p-trend = 0.03). Further research is needed to explore the association of melanoma with citrus juices among women with high sun exposure.

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Keywords

vegetables and fruit; diet; cohort study; epidemiology; cancer risk

Introduction:

The incidence of melanoma, the most dangerous form of skin cancer, has steadily risen in the US over the past 30 years (1). Exposure to ultraviolet (UV) radiation is the only well-established modifiable risk factor for melanoma (2). The association between UV and melanoma is complex (3), and the role of UV in melanoma pathogenesis is modified by other factors such as skin type, hair color, genetic factors, geographic location (3, 4), and even certain dietary factors (5–7). In our recent work we found that greater consumption of citrus products was associated with greater risk of incident basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (8) as well as melanoma (9) among men and women of the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). This association was not observed with consumption of non-citrus fruit and juice, however, suggesting that citrus products uniquely conferred this risk. One distinguishing characteristic common among many citrus products, and rather rare among most other fruits and vegetables, is their contents of furocoumarins.

Furocoumarins are a class of organic compounds produced by several plant species in response to stress and as a defense against predators (10). These photoactive compounds have been utilized in combination with UVA radiation in a phototherapy known as PUVA (psoralen and UVA) to treat proliferative skin diseases such as psoriasis. Upon photoactivation, furocoumarins may form cross-links with DNA, thereby disrupting cellular replication (11). While PUVA is effective for clearing psoriasis, it has been classified as a carcinogen (12), as its use has been shown to cause dose-dependent increases in the risk of BCC, SCC (13), and melanoma (14).

It is generally believed that citrus products are the primary source of furocoumarins in most American diets, as many citrus products are particularly rich sources of furocoumarins (15), and are commonly consumed as nutrient-dense food choices. Therefore, given the photocarcinogenic potential of furocoumarins, it has been hypothesized that citrus consumption may be associated with melanoma risk. Our preliminary investigation in men and women of the HPFS and NHS supports this hypothesis and suggested a synergistic effect between furocoumarins and UV radiation. However, the generalizability of these findings may be limited, as the populations represented in these cohorts are well-educated health professionals whose dietary habits and other health-related behaviors may differ from the general public. Therefore, additional investigation is needed to examine this hypothesis. Thus, the objective of this study was to evaluate the association of baseline citrus consumption with melanoma risk in the Women's Health Initiative (WHI), a large prospective cohort of postmenopausal women.

Methods:

Study population

The study population consisted of participants from the WHI Observational Study (OS). The overall study design of the WHI has been documented elsewhere (16). The WHI-OS enrolled postmenopausal women aged 50–79 years at baseline from 40 clinical centers throughout the United States between 1993 and 1998 (17). While the initial study period ended in 2005, WHI Extension Studies have continued follow-up of all women with consent. For this study, follow-up data were available through February 2017. Given their low incidence of melanoma, non-white participants (n = 12,565) were excluded from this analysis. Those with a prior history of melanoma (n = 1,211), any cancer at baseline other than non-melanoma skin cancer (NMSC) (n = 11,022), missing food frequency questionnaire (FFQ) data (n = 3,239), and missing information on sun exposure variables (n = 9,434) were also excluded, yielding an analytic cohort of 56,205 women.

Assessment of dietary consumption and other risk factors

In baseline FFQs, participants were asked how often they consumed various foods during the past 3 months. Participants were asked how often (in 9 categories ranging from never to 2+ servings per day) they had consumed “oranges, grapefruits, and tangerines” (1 orange or ½ grapefruit), which was used to assess citrus fruit consumption in this study. Participants were also asked how often they consumed “orange juice and grapefruit juice” (6 ounce glass), which was used to assess citrus juice consumption. Total citrus was calculated as the sum of reported frequencies of consuming citrus fruit and citrus juices. Total non-citrus fruit and juice consumption was estimated by summing the reported frequencies for 12 other items on the FFQ that inquired about non-citrus fruit products. Information on other dietary factors such as total energy intake, coffee consumption, and alcohol intake were also collected using the FFQ. Dietary intake collected using the FFQ has previously been validated against 24-hour dietary recalls and 4-day food records for estimation of 30 nutrients in a subset of participants (18). For most nutrients, mean intake estimated by the FFQ was within 10% of that estimated by food records or recalls.

In baseline questionnaires participants were asked about lifestyle factors including cigarette smoking, physical activity, and postmenopausal hormone use. Data on several variables related to skin cancer risk were also collected including skin reaction to the sun (tan vs. burn), use of sunscreen, and average daily time spent outdoors in summer as a child and currently. Sun exposure in Langleys of the participant’s clinical center was also recorded. These potential confounders as well as dietary habits were defined using baseline values.

Ascertainment of melanoma cases

At the time of entry into the study, each woman was asked whether she had ever been diagnosed with cancer, and if so, what type(s) of cancer. Women were also mailed questionnaires annually to report new health information including new cancer diagnoses. Reports of melanoma (and other cancers except for NMSC) were confirmed by physicians through medical record review in a central adjudication process, as has been described elsewhere (19, 20).

Statistical analysis

SAS software version 9.2 (SAS Institute, Cary, NC) was used for all statistical analyses. Chi-square tests of association for categorical variables and one-way ANOVA for continuous variables were used to examine differences in variables of interest between participants with differing levels of citrus consumption. All statistical tests were two-tailed, and the significance level was set at $P < 0.05$.

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of melanoma associated with dietary consumption of total citrus, citrus fruit, citrus juice, and non-citrus fruit and juice. Each participant contributed person-time from the time of the baseline questionnaire until the date of first diagnosis of any cancer, death, or the end of follow-up. Both age-adjusted and multivariable-adjusted models were tested. Multivariable models were adjusted for clinically important confounders including age, body mass index (BMI), education, physical activity, alcohol consumption, history of NMSC, regional solar radiation, skin reaction to sun, average daily time outdoors in summer currently, and sunscreen use. Models that additionally adjusted for total calorie intake, coffee consumption, smoking status, use of postmenopausal hormone replacement therapy, and average daily time outdoors in summer as a child did not generate materially different results and are therefore not presented. Trend tests across categories of dietary consumption were performed by assigning median values for these categories and treating the new variable as a continuous term in the models.

Supplemental analyses were conducted to explore potential differences in associations between citrus and melanoma among subgroups of participants. We performed subgroup analyses stratified by variables that showed evidence of interaction with citrus consumption. In subgroup analyses, multivariable adjusted HRs with 95% CIs were calculated.

Results:

Total citrus intake varied significantly by several demographic and lifestyle characteristics in this population. Participants with higher total citrus consumption tended to be older, had lower BMIs, had a higher total energy intake, had more education, and consumed more alcohol than those with lower total citrus consumption (Table 1). Several sun-related factors also varied by citrus consumption level. Those who consumed the most citrus reported spending more time outdoors in the summer during childhood and currently. Higher citrus consumers were also higher users of sunscreen and frequently reported having a skin type prone to tanning without burning.

During an average follow-up of 15.7 years, 956 melanoma cases were documented. Total citrus consumption was not significantly associated with incident melanoma in both age- and multivariable-adjusted models (Table 2). The age-adjusted HR among the participants in the highest citrus consumption category (1.5+ servings per day) compared to the lowest consumers (<2 servings/week) was 1.24 (95% CI: 1.01, 1.51) (p-trend = 0.05), and the multivariable-adjusted HR was 1.12 (95% CI: 0.91, 1.37). Citrus juice consumption showed a positive association with incident melanoma risk in the age-adjusted model, but not in the multivariable-adjusted model. In the age-adjusted model, the HR for incident melanoma among the highest citrus juice consumers (1+ servings/day), using the lowest consumers (<1 serving/week) as a reference, was 1.21 (95% CI: 1.03, 1.41) (p-trend = 0.01). After full adjustment, the HR among the highest citrus juice consumers, using the lowest consumers as a reference, was 1.13 (95% CI: 0.96, 1.32) (p-trend = 0.11). Citrus fruit consumption was not associated with melanoma risk, nor was consumption of non-citrus fruits and juices.

In subgroup analyses of women stratified by skin type, regional solar radiation, time outdoors in summer currently, sunscreen use, and history of NMSC, total citrus consumption was not significantly associated with risk of incident melanoma in any subgroups (Table 3). However, citrus juice consumption was significantly associated with increased melanoma risk among women who spent more than 30 minutes per day outdoors in the summer as adults (Table 4). Among these women, HRs for those consuming 1 serving/wk, 2–4 servings/wk, 5–6 servings/wk, and 1+ servings/day of citrus juice, using those consuming <1 serving/wk as a reference, were 0.90 (0.67, 1.20), 0.94 (0.75, 1.18), 1.04 (0.76, 1.44), and 1.22 (1.02, 1.46), respectively (p-trend = 0.03). No statistically significant trends in HRs were noted for citrus juice consumption among subgroups of skin reaction to the sun, regional solar radiation level, history of NMSC, or sunscreen use.

Discussion:

In this prospective cohort study of postmenopausal women there was no clear association between citrus consumption and risk of incident melanoma. The data suggested that citrus fruit juice consumption may be more closely associated with melanoma risk than total citrus consumption, yet this trend was not statistically significant when adjusted for important confounders. Subgroup analyses indicated that citrus juice consumption was associated with an increased melanoma risk among women who spent the most time outdoors in summer as adults.

These results somewhat differ from the findings of our previous work documenting a positive association between total citrus consumption and melanoma risk in the HPFS and NHS (9). Discrepancies between these studies could be related to various factors. If a relationship between citrus consumption and melanoma risk exists, and if the relationship is related to furocoumarin exposure, the use of total citrus as a crude indicator of furocoumarin consumption may reduce the ability to detect significant relationships in this study. Although citrus products are collectively believed to be the major source of furocoumarins in the American diet, there is wide variability in furocoumarin concentrations between individual citrus products. In our previous work we documented that the total concentration of seven furocoumarin compounds varied from 21858 ng/g in grapefruit, to 9151 ng/g in limes, to 0.5 ng/g in oranges (15). Furthermore, individual citrus products vary widely in the concentrations of individual furocoumarin compounds. For example, grapefruits are particularly rich in bergamottin and 6′7′-dihydroxybergamottin (6′7′-DHB), but limes exceed grapefruits in their concentrations of bergaptol and bergapten (15). While the NHS and HPFS asked separate questions on grapefruits, grapefruit juice, oranges, and orange juice, WHI participants reported consumption of oranges, grapefruits, and tangerines together, and orange juice and grapefruit juice together, which did not allow us to evaluate these items separately. Furthermore, other major citrus products that are rich in

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furocoumarins, such as lemons and limes, were not assessed in the FFQ used in the WHI. Therefore, assessment of total citrus consumption using the WHI FFQ is an imperfect approach for examining a potential relationship between furocoumarin consumption and melanoma risk.

Nonetheless, the results of the present study suggested that higher consumption of citrus juices may be associated with incident melanoma among women spending at least 30 minutes outdoors daily during the summer as adults. This study included several sub-analyses examining multiple citrus products and participant subgroups, which could result in false positive findings due to chance. However, the association observed in women spending more time outdoors suggests a potential synergistic interaction between furocoumarins and UV radiation, which is consistent with our hypothesis based on previous data. Interestingly, we found no association between consumption of whole fruits and melanoma risk. This may be related in part to the differing furocoumarin profiles and concentrations between whole citrus fruits and their juices (15, 21, 22). Furocoumarins that are normally found primarily in the peel of citrus fruits may be distributed into the processed fruit juice through the squeezing process (22). Given that various furocoumarin compounds differ in their cytotoxic and carcinogenic potentials (23, 24), the different furocoumarin profiles of citrus fruit compared to juice may therefore contribute to some differences in associated risk observed in this study. However, further research is needed to ascertain which specific furocoumarin compounds may impact skin cancer risk in humans, and whether the amounts consumed in typical diets can meaningfully affect risk.

While citrus consumption was not found to be associated with incident melanoma risk in this study, our data, along with findings of previous human and animal studies, suggest a need for further investigation of a potential relationship between citrus and skin cancer risk, especially among women who have high sun exposure. Human studies including both men and women, and using long-term follow-up and detailed dietary data collection methods will be essential for understanding any public health risk associated with citrus products or dietary furocoumarins. Additional cellular and animal studies are needed to clarify whether certain furocoumarin compounds found in citrus products may meaningfully impact skin cancer risk in humans and to further clarify the underlying mechanisms.

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Table 1.

Baseline characteristics of participants according to frequency of total citrus consumption (medium serving size)

	Total Citrus Intake							
Level	***<2/wk***	***2–4/wk***	***5–6/wk***	***1–1.4/d***	***1.5+/d***	**Total**	**p-value**	**trend p-value**
N (%)	15,947 (28.4)	12,386 (22.0)	5,744 (10.2)	13,702 (24.4)	8,426 (15.0)	56,205		
Median intake/day	0.08767	0.5000	0.77808	1.07671	1.72329			
Citrus Fruit, daily medium servings (*mean, SD*)	0.063 (0.076)	0.214 (0.182)	0.381 (0.261)	0.400 (0.373)	0.808 (0.690)	0.323 (0.424)	<0.001	<0.001
Citrus Juice, daily medium servings (*mean, SD*)	0.048 (0.068)	0.276 (0.191)	0.396 (0.268)	0.701 (0.377)	1.163 (0.660)	0.460 (0.511)	<0.001	<0.001
Non-Citrus Fruit and Juice, daily medium servings (*mean, SD*)	1.655 (1.344)	1.817 (1.233)	1.997 (1.290)	2.053 (1.347)	2.588 (1.885)	1.963 (1.444)	<0.001	<0.001
Age (*yrs*)	62.3 (7.1)	63.3 (7.1)	63.4 (7.2)	64.3 (7.1)	64.0 (7.3)	63.4 (7.2)	<0.001	<0.001
NMSC at baseline (*n, %*)	1956 (12.3)	1516 (12.2)	742 (12.9)	1861 (13.6)	1123 (13.3)	7198 (12.8)		
Regional solar radiation Langleys (g-cal/cm^2) *(n, %)*							<0.001	
300–325	4580 (28.7)	4059 (32.8)	1923 (33.5)	4914 (35.9)	2933 (34.8)	18409 (32.8)		
350	3110 (19.5)	2483 (20.1)	1172 (20.4)	3031 (22.1)	1999 (23.7)	11795 (21.0)		
375–380	1776 (11.1)	1400 (11.3)	602 (10.5)	1500 (11.0)	895 (10.6)	6173 (11.0)		
400–430	3051 (19.1)	2027 (16.4)	917 (16.0)	1859 (13.6)	1113 (13.2)	8967 (16.0)		
475–500	3430 (21.5)	2417 (19.5)	1130 (19.7)	2398 (17.5)	1486 (17.6)	10861 (19.3)		
Average daily time outdoors in summer as a child *(n, %)*							<0.001	
<30 minutes	375 (2.4)	270 (2.2)	119 (2.1)	281 (2.1)	178 (2.1)	1223 (2.2)		
30 min to 2 hours	4132 (25.9)	3362 (27.1)	1431 (24.9)	3614 (26.4)	2032 (24.1)	14571 (25.9)		
2+ hours	11440 (71.7)	8754 (70.7)	4194 (73.0)	9807 (71.6)	6216 (73.8)	40411 (71.9)		
Average daily time outdoors in summer currently *(n, %)*							<0.001	
<30 minutes	5302 (33.3)	3680 (29.7)	1580 (27.5)	3944 (28.8)	2367 (28.1)	16873 (30.0)		
30 min to 2 hours	7741 (48.5)	6344 (51.2)	3020 (52.6)	7104 (51.9)	4154 (49.3)	28363 (50.5)		
2+ hours	2904 (18.2)	2362 (19.1)	1144 (19.9)	2654 (19.4)	1905 (22.6)	10969 (19.5)		
Sunscreen SPF *(n, %)*								
None	8156 (51.1)	5618 (45.4)	2548 (44.4)	6055 (44.2)	3666 (43.5)	26043 (46.3)		
Something but don't know	230 (1.4)	173 (1.4)	78 (1.4)	189 (1.4)	115 (1.4)	785 (1.4)		
2–14	738 (4.6)	657 (5.3)	311 (5.4)	684 (5.0)	414 (4.9)	2804 (5.0)		
15–24	4301 (27.0)	3752 (30.3)	1812 (31.6)	4389 (32.0)	2686 (31.9)	16940 (30.1)		
25+	2522 (15.8)	2186 (17.7)	995 (17.3)	2385 (17.4)	1545 (18.3)	9633 (17.1)		

Level	Total Citrus Intake					Total		trend
	<2/wk	*2–4/wk*	*5–6/wk*	*1–1.4/d*	*1.5+/d*			
Skin reaction to sun *(n, %)*							0.010	
No change	955 (6.0)	730 (5.9)	342 (6.0)	779 (5.7)	461 (5.5)	3267 (5.8)		
Tans, does not burn	4649 (29.2)	3707 (29.9)	1709 (29.8)	4063 (29.7)	2609 (31.0)	16737 (29.8)		
Burns, then tans	4045 (25.4)	3157 (25.5)	1501 (26.1)	3591 (26.2)	2173 (25.8)	14467 (25.7)		
Burns, then tans minimally	4344 (27.2)	3423 (27.6)	1563 (27.2)	3787 (27.6)	2235 (26.5)	15352 (27.3)		
Burns, does not tan	1954 (12.3)	1369 (11.1)	629 (11.0)	1482 (10.8)	948 (11.3)	6382 (11.4)		
Education *(n, %)*							<0.001	
< high school graduate	590 (3.7)	352 (2.8)	131 (2.3)	282 (2.1)	166 (2.0)	1521 (2.7)		
high school graduate	2978 (18.7)	1986 (16.0)	899 (15.7)	1977 (14.4)	1116 (13.2)	8956 (15.9)		
some college	5988 (37.6)	4602 (37.2)	1939 (33.8)	4682 (34.2)	2869 (34.1)	20080 (35.7)		
college graduate	6262 (39.3)	5368 (43.3)	2743 (47.8)	6676 (48.7)	4217 (50.1)	25266 (45.0)		
BMI, kg/m2 *(mean, SD)*	27.3 (6.0)	27.0 (5.8)	27.0 (5.7)	26.6 (5.6)	26.6 (5.8)	26.9 (5.8)	<0.001	<0.001
Physical activity *(n, %)*							<0.001	
Inactive (0–1.7)	3482 (22.1)	1976 (16.1)	839 (14.7)	2020 (14.9)	1091 (13.1)	9408 (16.9)		
Low Activity (1.8–8.3)	4336 (27.5)	3275 (26.7)	1460 (25.7)	3322 (24.5)	1935 (23.1)	14328 (25.7)		
Mod Activity (8.4–20)	4487 (28.4)	3880 (31.6)	1784 (31.3)	4481 (33.0)	2665 (31.9)	17297 (31.1)		
High Activity (>20)	3476 (22.0)	3156 (25.7)	1609 (28.3)	3740 (27.6)	2670 (31.9)	14651 (26.3)		
Cigarette smoking status *(n, %)*							<0.001	
Never	7295 (46.3)	6202 (50.6)	2918 (51.4)	7030 (52.0)	4401 (52.8)	27846 (50.2)		
Past	7216 (45.8)	5420 (44.3)	2517 (44.3)	5974 (44.2)	3578 (43.0)	24705 (44.5)		
Current	1232 (7.8)	627 (5.1)	247 (4.4)	521 (3.9)	351 (4.2)	2978 (5.4)		
Alcohol consumption, g/day *(mean, SD)*	5.77 (11.68)	6.23 (11.26)	6.57 (12.07)	6.74 (11.38)	6.50 (11.41)	6.30 (11.52)	<0.001	<0.001
Coffee consumption, cups/day *(mean, SD)*	2.26 (1.83)	2.22 (1.73)	2.24 (1.71)	2.14 (1.62)	2.13 (1.70)	2.20 (1.73)	<0.001	<0.001
Hormone Therapy status (*n, %*)							<0.001	
Never	3934 (25.1)	3210 (26.4)	1499 (26.7)	3734 (27.8)	2401 (29.1)	14778 (26.8)		
Past	3049 (19.4)	2299 (18.9)	1070 (19.0)	2632 (19.6)	1557 (18.8)	10607 (19.2)		
Current	8704 (55.5)	6675 (54.8)	3051 (54.3)	7064 (52.6)	4307 (52.1)	29801 (54.0)		

Table 2.

Hazard ratios for incident melanoma according to frequency of citrus consumption

	Serving Category					P for trend
Total Citrus	<2/wk	2–4/wk	5–6/wk	1–1.4/d	1.5+/d	
No. of person-years	248,899	193,710	90,868	216,254	132,152	
No. of cases	245	224	85	243	159	
Age-adjusted HR (95% CI)	(ref)	1.18 (0.99, 1.42)	0.96 (0.75, 1.22)	1.16 (0.97, 1.38)	1.24 (1.01, 1.51)	0.05
Multivariable-adjusted HR (95% CI)	(ref)	1.14 (0.95, 1.37)	0.90 (0.70, 1.16)	1.06 (0.88, 1.28)	1.12 (0.91, 1.37)	0.45
Citrus Juice	<1/wk	1/wk	2–4/wk	5–6/wk	1+/d	
No. of person-years	382,946	78,667	148,035	53,658	218,576	
No. of cases	402	72	145	62	275	
Age-adjusted HR (95% CI)	(ref)	0.87 (0.68, 1.12)	0.95 (0.78, 1.14)	1.10 (0.85, 1.44)	1.21 (1.03, 1.41)	0.01
Multivariable-adjusted HR (95% CI)	(ref)	0.86 (0.67, 1.11)	0.95 (0.78, 1.15)	1.08 (0.82, 1.42)	1.13 (0.96, 1.32)	0.11
Citrus Fruit	Never	<1/wk	1/wk	2–4/wk	5+/wk	
No. of person-years	146,291	338,313	114,702	124,254	158,323	
No. of cases	143	384	129	133	167	
Age-adjusted HR (95% CI)	(ref)	1.15 (0.95, 1.40)	1.15 (0.90, 1.46)	1.10 (0.87, 1.39)	1.09 (0.87, 1.36)	0.87
Multivariable-adjusted HR (95% CI)	(ref)	1.05 (0.86, 1.28)	1.03 (0.81, 1.31)	0.97 (0.76, 1.23)	0.95 (0.76, 1.20)	0.44
Non-Citrus Fruit/Juice	<0.75/d	0.75–1.2/d	1.3–1.9/d	2.0–2.9/d	3+/d	
No. of person-years	143,368	180,183	212,029	192,722	153,580	
No. of cases	155	187	229	215	170	
Age-adjusted HR (95% CI)	(ref)	0.96 (0.78, 1.19)	1.00 (0.82, 1.23)	1.04 (0.85, 1.28)	1.04 (0.83, 1.29)	0.52
Multivariable-adjusted HR (95% CI)	(ref)	0.92 (0.73, 1.14)	0.90 (0.73, 1.11)	0.92 (0.74, 1.14)	0.92 (0.73, 1.15)	0.63

Multivariable-adjusted HRs were adjusted for age (continuous), BMI (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m2), education (less than high school graduate, high school graduate, some college, college graduate), physical activity (inactive, low activity, moderate activity, high activity), alcohol consumption (continuous), history of NMSC (yes, no), regional solar radiation (300–325, 350, 375–380, 400–430, 475–500 Langleys), skin reaction to sun (no burns, with or without tanning; burns, with or without tanning), average daily time outdoors currently (<30min, 30min - 2hrs, 2+ hrs), and sunscreen SPF use (none, something but don't know, SPF 2–14, SPF 15–24, SPF 25+)

Table 3.

Multivariable hazard ratios for incident melanoma according to frequency of total citrus consumption in subgroups of potential confounders

	Total Citrus Serving Category					P for trend
	<2/wk	2–4/wk	5–6/wk	1–1.4/d	1.5+/d	
Time Outdoors in Summer Currently						
< 30 minutes/day						
Number of person-years	80,406	55,199	23,766	59,672	35,652	
Number of cases	70	64	20	59	31	
Multivariable Adjusted HR (95% CI)	(ref)	1.38 (0.98, 1.96)	0.92 (0.55, 1.54)	1.08 (0.75, 1.55)	1.00 (0.64, 1.54)	0.76
> 30 minutes/day						
Number of person-years	168,494	138,511	67,102	156,581	96,499	
Number of cases	175	160	65	184	128	
Multivariable Adjusted HR (95% CI)	(ref)	1.06 (0.85, 1.33)	0.89 (067, 1.19)	1.05 (0.85, 1.30)	1.15 (0.91, 1.46)	0.29
Skin reaction to sun						
No burn, with or without tanning						
Number of person-years	84,832	67,067	31,553	74,619	46,685	
Number of cases	64	45	20	52	33	
Multivariable Adjusted HR (95% CI)	(ref)	0.81 (0.54, 1.20)	0.75 (0.45, 1.26)	0.86 (0.59, 1.27)	0.85 (0.55, 1.31)	0.51
Burn, with or without tanning						
Number of person-years	164,067	126,643	59,315	141,634	85,466	
Number of cases	181	179	65	191	126	
Multivariable Adjusted HR (95% CI)	(ref)	1.25 (1.01, 1.55)	0.95 (0.71, 1.27)	1.14 (0.92, 1.40)	1.21 (0.95, 1.53)	0.24
Regional solar radiation						
300–350						
Number of person-years	121,819	103,326	49,609	125,681	78,120	
Number of cases	109	120	46	148	93	
Multivariable Adjusted HR (95% CI)	(ref)	1.24 (0.95, 1.62)	0.97 (0.68, 1.37)	1.19 (0.92, 1.54)	1.18 (0.89, 1.57)	0.34
375–500						
Number of person-years	127,080	90,384	41,259	90,572	54,032	
Number of cases	136	104	39	95	66	
Multivariable Adjusted HR (95% CI)	(ref)	1.06 (0.82, 1.38)	0.86 (0.60, 1.23)	0.93 (0.71, 1.22)	1.08 (0.80, 1.46)	0.96
History of NMSC						
No history of NMSC						
Number of person-years	219,598	170,986	79,718	187,597	114,993	
Number of cases	180	168	68	174	121	

		Total Citrus Serving Category				P for trend
Multivariable Adjusted HR (95% CI)	(ref)	1.19 (0.96, 1.48)	1.01 (0.76, 1.34)	1.09 (0.88, 1.36)	1.19 (0.94, 1.51)	0.28
History of NMSC						
Number of person-years	29,302	22,724	11,150	28,657	17,159	
Number of cases	65	56	17	69	38	
Multivariable Adjusted HR (95% CI)	(ref)	0.99 (0.68, 1.44)	0.59 (0.34, 1.04)	1.00 (0.70, 1.42)	0.91 (0.60, 1.38)	0.70
Sunscreen Use						
No sunscreen use						
Number of person-years	125,067	86,502	39,582	93,478	56,387	
Number of cases	92	65	24	79	42	
Multivariable Adjusted HR (95% CI)	(ref)	1.04 (0.75, 1.43)	0.77 (0.48,1.21)	1.07 (0.78, 1.47)	0.93 (0.64, 1.36)	0.82
Sunscreen use (any or unknown SPF)						
Number of person-years	123,833	107,208	51,285	122,776	75,765	
Number of cases	153	159	61	164	117	
Multivariable Adjusted HR (95% CI)	(ref)	1.20 (0.95, 1.50)	0.98 (0.72, 1.32)	1.06 (0.84, 1.33)	1.21 (0.94, 1.55)	0.30

Multivariable-adjusted HRs were adjusted for age (continuous), BMI (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m2), education (less than high school graduate, high school graduate, some college, college graduate), physical activity (inactive, low activity, moderate activity, high activity), alcohol consumption (continuous), history of NMSC (yes, no), regional solar radiation (300–325, 350, 375–380, 400–430, 475–500 Langleys), skin reaction to sun (no burns, with or without tanning; burns, with or without tanning), average daily time outdoors currently (<30min, 30min - 2hrs, 2+ hrs), and sunscreen SPF use (none, something but don't know, SPF 2–14, SPF 15–24, SPF 25+). For each stratified analysis, stratifying variable was omitted from models.

Table 4.

Multivariable hazard ratios for incident melanoma according to frequency of citrus juice consumption in subgroups of potential confounders

	Citrus Juice Serving Category					P for trend
	<1/wk	1/wk	2–4/wk	5–6/wk	1+/d	
Time Outdoors in Summer Currently						
< 30 minutes/day						
Number of person-years	115,599	21,897	41,364	14,778	61,058	
Number of cases	116	17	39	17	55	
Multivariable Adjusted HR (95% CI)	(ref)	0.77 (0.46, 1.30)	0.97 (0.67, 1.40)	1.21 (0.72, 2.01)	0.87 (0.63, 1.21)	0.60
> 30 minutes/day						
Number of person-years	267,348	56,770	106,671	38,880	157,518	
Number of cases	286	55	106	45	220	
Multivariable Adjusted HR (95% CI)	(ref)	0.90 (0.67, 1.20)	0.94 (0.75, 1.18)	1.04 (0.76, 1.44)	1.22 (1.02, 1.46)	0.03
Skin reaction to sun						
No burn, with or without tanning						
Number of person-years	132,179	26,558	53,320	18,171	74,530	
Number of cases	93	13	36	13	59	
Multivariable Adjusted HR (95% CI)	(ref)	0.69 (0.38, 1.27)	1.05 (0.71, 1.56)	1.00 (0.54, 1.83)	1.13 (0.81, 1.60)	0.41
Burn, with or without tanning						
Number of person-years	250,768	52,109	94,715	35,488	144,045	
Number of cases	309	59	109	49	216	
Multivariable Adjusted HR (95% CI)	(ref)	0.90 (0.68, 1.20)	0.91 (0.73, 1.14)	1.10 (0.81, 1.50)	1.13 (0.95, 1.35)	0.15
Regional solar radiation						
300–350						
Number of person-years	190,606	43,109	84,557	29,262	131,020	
Number of cases	190	38	86	28	174	
Multivariable Adjusted HR (95% CI)	(ref)	0.85 (0.60, 1.21)	1.01 (0.78, 1.31)	0.94 (0.63, 1.39)	1.21 (0.98, 1.49)	0.08
375–500						
Number of person-years	192,340	35,557	63,478	24,396	87,556	
Number of cases	212	34	59	34	101	
Multivariable Adjusted HR (95% CI)	(ref)	0.87 (0.60, 1.26)	0.87 (0.65, 1.17)	1.25 (0.86, 1.82)	1.01 (0.80, 1.29)	0.74
History of NMSC						
No history of NMSC						
Number of person-years	336,355	69,816	129,904	47,389	189,429	
Number of cases	297	54	112	46	202	

		Citrus Juice Serving Category				P for trend
Multivariable Adjusted HR (95% CI)	(ref)	0.88 (0.66, 1.18)	0.99 (0.80, 1.24)	1.08 (0.79, 1.48)	1.14 (0.95, 1.37)	0.13
History of NMSC						
Number of person-years	46,591	8,851	18,131	6,270	29,147	
Number of cases	105	18	33	16	73	
Multivariable Adjusted HR (95% CI)	(ref)	0.80 (0.47, 1.35)	0.81 (0.54, 1.21)	1.03 (0.59, 1.81)	1.09 (0.80, 1.49)	0.55
Sunscreen Use						
No sunscreen use						
Number of person-years	182,539	34,102	66,289	23,824	94,262	
Number of cases	133	21	47	22	79	
Multivariable Adjusted HR (95% CI)	(ref)	0.89 (0.56, 1.41)	1.00 (0.71, 1.40)	1.20 (0.75, 1.90)	1.08 (0.81, 1.44)	0.49
Sunscreen use (any or unknown SPF)						
Number of person-years	200,408	44,564	81,746	29,835	124,313	
Number of cases	269	51	98	40	196	
Multivariable Adjusted HR (95% CI)	(ref)	0.85 (0.63, 1.15)	0.92 (0.73, 1.17)	1.02 (0.73, 1.43)	1.14 (0.95, 1.38)	0.15

Multivariable-adjusted HRs were adjusted for age (continuous), BMI (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m2), education (less than high school graduate, high school graduate, some college, college graduate), physical activity (inactive, low activity, moderate activity, high activity), alcohol consumption (continuous), history of NMSC (yes, no), regional solar radiation (300–325, 350, 375–380, 400–430, 475–500 Langleys), skin reaction to sun (no burns, with or without tanning; burns, with or without tanning), average daily time outdoors currently (<30min, 30min - 2hrs, 2+ hrs), and sunscreen SPF use (none, something but don't know, SPF 2–14, SPF 15–24, SPF 25+). For each stratified analysis, stratifying variable was omitted from models.